I. Relying on 35 U.S.C. § 103, Claims 51-55 and 57-61 were rejected by the Examiner as being unpatentable over Sanders et al. in view of Alberts et al or Watson et al., all further in view of Axel et al..

Applicants traverse this rejection as previously applied for the following reasons.

Applicants respectfully submit that none of the cited references teach a vector encoding a complete glutamine synthetase (GS) gene as an amplifiable unit or an amplifiable vector. On page 3 of the Official Action, the Examiner asserts that the Axel et al. patent, which is assumed to be enabled and accurate, was issued prior to the disclosure of Sanders et al. and discloses amplifiable vectors containing a mutant DHFR gene and heterologous DNAs, host cells transformed with said vectors, a method for introducing and amplifying nonselectable genes into host cells, use of the mutant dhfr gene as a dominant selectable marker, etc. The Examiner asserts that it is unclear if the vectors disclosed by Axel et al. contain a complete dhfr gene, although Axel et al. refers to transfer of the amplifiable mutant dhfr gene and it can be assumed that a complete, amplifiable, dhfr gene was involved.

Applicants respectfully submit that the teachings of Axel et al. and the other cited references do not overcome the lack of disclosure in the prior art of a complete

H

mammalian GS gene because none of the cited references provide the motivation nor the means to clone the **complete** GS gene. Applicants reiterate that Sanders et al. is an academic paper relating to an investigation of the GS gene in CHO cells. Sanders et al. show that the genomic GS gene can be amplified by selecting CHO cells resistant to increasing levels of Msx. Sanders et al. also purportedly reports the partial cloning of the GS gene (see below). However, Sanders et al. do not show the cloning of the complete GS gene, nor does it in any way relate to the use of the GS gene as a selectable marker or in co-amplification processes.

In particular, Applicants respectfully submit that the Sanders et al. paper points away from the use of a GS gene in the above processes. The fact that the endogenous gene in CHO cells can be amplified in its natural chromosomal environment would lead a skilled artisan to expect that the amplification of the endogenous gene would prevent selection of transformants containing an amplified exogenous GS gene. Applicants simply fail to see how a skilled artisan could gain any incentive from Sanders et al. even to consider using a GS gene as a tool in recombinant DNA technology, let alone in the specific methods now claimed.

In this regard, Applicants note that Examiner has stated that the motivation for combining the cited references is the "potential use in coamplifying an additional foreign gene of

interest." Applicants cannot find this motivation the cited references. Rather, Applicants respectfully submit that this alleged motivation for this "potential" is first disclosed in their specification. Applicants respectfully submit that such use of their disclosure in formulating a rejection is improper hindsight on the part of the Examiner.

Applicants respectfully direct the Examiner to claims 21 and 22 of U.S. Patent 5,122,464. This patent corresponds to U.S. Application 07/595,733 which is the parent of the instant application. Claims 21 and 22 read:

"21. A plasmid including the GS minigene from plasmid pSVLGS.1.

22. A plasmid including the SV40-GS transcription unit from plasmid pSVLGS.1".

As discussed in the interview of February 22, 1996, the subject plasmids of claims 21 and 22 of the 5,122,464 patent already claim a complete mammalian GS gene. Please also note that the plasmids of instant claims 53 and 54 are produced by inserting the gene encoding tPA into pSVLGS.1 (see page 33). Applicants respectfully submit that since claims directed to plasmids encoding a complete mammalian GS gene have already been allowed in the parent application, the rejection of the instant claims over the cited references should be withdrawn.

Applicants also assert that there is nothing in the cited references to suggest the advantage of the instant

vectors with regard to their ability to amplify the GS gene and a foreign gene in cells containing an endogenous GS gene. In response, the Examiner notes that this limitation is not recited in the claims. The Examiner illustrates an example by noting Claim 51.

Applicants respectfully submit that the unexpected ability to amplify the GS gene of the claimed vectors in cells which contain an endogenous GS gene is in itself grounds for withdrawal of the instant rejection. Applicants again submit that the ability to amplify GS on the claimed vectors in cells which possess an endogenous GS gene is the **only motivation** present to produce the claimed vectors. This motivation can be found **only** in the instant specification.

In contrast to the results of the instant specification, Sanders et al. teach that the endogenous **chromosomally** encoded GS gene can be amplified. Applicants respectfully submit that this disclosure of Sanders et al. would **not** lead the skilled artisan to endeavor to clone the entire GS gene because amplification of the endogenous gene would prevent selection of transformants containing an amplified exogenous GS gene.

The Examiner asserts that Axel et al. teaches cells transfected with a vector containing a dhfr gene, wherein said cells contain an endogenous dhfr gene which is "complete" in that it is enzymatically active and only

differs from a wild-type gene in that it is a dominant acting methotrexate resistant gene..

Applicants respectfully submit that Axel et al. is directed to use of a mutant dhfr gene and that the teachings of Axel et al. are not relevant to the instantly claimed subject matter, which recites a **complete mammalian GS gene**. The cited references do not teach a complete GS gene and do not provide the motivation to clone said complete gene. Without the previous cloning of the complete GS gene or alternatively, the motivation and means to do so in the prior art, Applicants respectfully request withdrawal of the rejection of claim 51-55 and 57-61.

II. Claim 56 is rejected under 35 U.S.C. § 103 as being unpatentable over Ringold et al. (U.S. Patent No. 4,656,134) in view of Sanders et al. and Watson et al. or Alberts et al.. Applicants traverse this rejection and request withdrawal of the rejection in view of the following.

Claim 56 is directed to a method of endowing a cell (possessing reduced or non-existent GS activity) with the ability to survive in a medium lacking glutamine comprising transforming said cell with an amplifiable vector encoding a complete mammalian GS gene.

The Examiner asserts that Ringold et al. recites a method for endowing a cell deficient in DHFR with DHFR

activity "and hence the ability to survive in medium without glutamine" by transforming said cell with an amplifiable vector containing the DHFR gene. The Examiner then asserts that while Ringold et al. do not definitively recite transformation with a vector containing the entire DHFR gene, Ringold et al. do recite transfection with a DHFR gene encoding an enzymatically active enzyme and given the teachings of Sanders et al. on the isolation of at least part of the CHO DHFR gene and the teachings of Watson et al. or Alberts et al. on cloning of genes of interest, it must be considered that isolation of the entire DHFR gene by the ordinary skilled artisan would have been an obvious, routine, matter. The Examiner then concludes that given the routine nature of cloning procedures at the time the instant invention was made, it must be considered that the ordinary skilled artisan would have had a reasonable expectation of success in isolating the complete GS gene.

Applicants respectfully submit that the application of the cited art is improper for many of the reasons set forth above. First, Applicants do not understand how Ringold is held to recite a method for endowing a cell deficient in DHFR with DHFR activity and hence the ability to survive in medium without glutamine. Ringold uses a dominant mutant of DHFR which allows selection with methotrexate.

The Examiner is also directed the dependency of claim 56. Claim 56 is dependent upon claim 51, which recites that the vector encodes a **complete** mammalian GS gene.

As set forth above, claims 21 and 22 of U.S. Patent 5,122,464 patent (application serial No. 07/595,733) already claim a complete mammalian GS gene. Since the instant application claims priority to application No. 07/595,733, Applicants respectfully submit that the rejection of claim 56 cannot be maintained.

III. The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention.

The Examiner notes that Applicants recite a method of endowing a "CHO-KI myeloma cell" (claim 58) deficient in GS activity with the ability to survive in media lacking glutamine and asserts that there is no written description of a "CHO-KI myeloma cell" in the specification as filed.

Applicants respectfully submit that the amendment to Claim 58 overcomes this rejection.

IV. Relying on 35 U.S.C. § 112, first paragraph, the Examiner has objected to the specification as failing to adequately teach how to make and/or use myeloma cells in the method of claims 57 and 59. The Examiner then rejected

claims 57 and 59 under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

The Examiner asserts at the bottom of page 6 that the specification does not disclose which myeloma cells are suitable for use in the claimed method, how the cells are to be obtained, how myeloma cells are to be cultured and how mutant cell populations lacking GS activity are to be generated. Applicants respectfully submit that the Examiner has provided no reasoning or rationale why the claimed method would not work to endow myeloma cells lines with the ability to survive without added glutamine in the media.

Applicants further submit that the specification does not need to teach what is already known in the art. Myeloma cells lines have been produced and routinely used in scientific research for many years before the priority date of this application. As the Examiner is aware, myeloma cell lines were used as fusion partners to produce hybridomas as early as the mid-1970s (see Köhler et al.). It was also known in the art that many lymphoid cell lines, such as myeloma cell lines, require the addition of glutamine to the cell culture medium. For instance, in 1976, Roberts et al. published that the growth of myeloma cells in culture is limited by the depletion of glutamine and that this growth inhibition could be reversed by adding exogenous glutamine to the medium (see abstract). Accordingly, the ability to

obtain and culture myeloma cell lines which require glutamine was not a limiting factor at the time of the invention.

The Examiner asserts at page 7 of the Official Action that the specification does not cite relevant prior art that provides guidance to the skilled artisan. Applicants respectfully submit that the specification need not teach or disclose in detail that which is well known in the art. In re Myers, 161 USPQ 668, 671 (CCPA 1969). As the instant specification teaches that a mammalian GS gene can be successfully transfected, amplified and expressed within mammalian cells, even when the cell comprise an endogenous copy of GS, Applicants submit that no further showings are required and respectfully request that the rejection of claims 57 and 59 be withdrawn.

V. Claims 51 and 55 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regards as the invention.

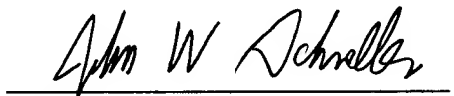
The Examiner asserts that claim 51 (and dependent Claim 55) are vague in that Applicants recite a DNA expression vector "...which is capable..." of expressing a GS gene.

Applicants thank the Examiner for the suggested claim language and respectfully submit that the amendment to claim 51 overcomes this rejection.

CONCLUSIONS

In view of the above discussion and Amendments, Applicants respectfully submit that the application is considered to be in condition for allowance. The Examiner is invited to call the undersigned attorney if any minor matter remains.

Respectfully submitted,



John W. Schneller
(Registration No. 26,031)
SPENCER & FRANK
1111 19th Street, N.W.
Washington, D.C. 20036
Telephone: (202) 828-8000
Telefacsimile: (202) 828-8038

JWS:MST:dvb